PATENT COOPERATION TREATY

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INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

REC'D 06 JUN 2005 WIPO PCT

Applicant's or agent's file reference 02469PXM	FOR FURTHER ACTION	See Form PCT/IPEA/416
International application No. PCT/AU2004/000856	International filing date *(day/month/year)* 28 June 2004	Priority date *(day/month/year)* 27 June 2003

International Patent Classification (IPC) or national classification and IPC

Int. Cl. [7] G01N 33/68, 33/574, 33/564, 33/569

Applicant

PROTEOME SYSTEMS INTELLECTUAL PROPERTY PTY LTD et al

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 7 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☐ *(sent to the applicant and to the International Bureau)* a total of sheets, as follows:
      ☐ sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or table related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).
4. This report contains indications relating to the following items:

☒	Box No. I	Basis of the report
☐	Box No. II	Priority
☐	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☐	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☐	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the international application
☒	Box No. VIII	Certain observations on the international application

Date of submission of the demand	Date of completion of the report
12 January 2005	23 May 2005
Name and mailing address of the IPEA/AU	Authorized Officer
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INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/AU2004/000856

Box No. I Basis of the report

1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.

☐ This report is based on translations from the original language into the following language , which is the language of a translation furnished for the purposes of:

☐ international search (under Rules 12.3 and 23.1 (b))

☐ publication of the international application (under Rule 12.4)

☐ international preliminary examination (under Rules 55.2 and/or 55.3)

2. With regard to the **elements** of the international application, this report is based on (*replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report*):

☒ the international application as originally filed/furnished

☒ the description:

pages **1-104** as originally filed/furnished
pages* received by this Authority on with the letter of
pages* received by this Authority on with the letter of

☒ the claims:

pages **105-129** as originally filed/furnished
pages* as amended (together with any statement) under Article 19
pages* received by this Authority on with the letter of
pages* received by this Authority on with the letter of

☒ the drawings:

pages **1/7-7/7** as originally filed/furnished
pages* received by this Authority on with the letter of
pages* received by this Authority on with the letter of

☒ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing.

3. ☐ The amendments have resulted in the cancellation of:

☐ the description, pages
☐ the claims, Nos.
☐ the drawings, sheets/figs
☐ the sequence listing (*specify*):
☐ any table(s) related to the sequence listing (*specify*):

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).

☐ the description, pages
☐ the claims, Nos.
☐ the drawings, sheets/figs
☐ the sequence listing (*specify*):
☐ any table(s) related to the sequence listing (*specify*):

* *If item 4 applies, some or all of those sheets may be marked "superseded."*

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims	28-33, 39-42, 59-64, 87-127, 153-160, 166, 173-192	YES
	Claims	1-27, 34-38, 43-58, 65-86, 128-152, 161-165, 167-172, 193-198	NO
Inventive step (IS)	Claims	175-192	YES
	Claims	1-174, 193-198	NO
Industrial applicability (IA)	Claims	1-198	YES
	Claims		NO

2. Citations and explanations (Rule 70.7)

This invention relates to a method for identifying and isolating proteins from a biological sample which contains a protein complex comprising an immunoglobulin and a protein bound to the immunoglobulin wherein the protein is separated from the immunoglobulin. Such isolated proteins or peptide fragments were found to be immunogenic. The method may be used to identify a protein against which a subject has raised an immune response, for example, in a subject with cancer, an autoimmune condition, an infection such as Mycobacterium tuberculosis or Pseudomonas aeruginosa. It is proposed that the isolated proteins may be useful for developing therapeutic or prophylactic strategies for the treatment of a disease or infection.

The following documents were regarded as relevant in the ISR:

D1: US 5,932,705

D2: US 5,116,766

D3: US 6,416,962

D4: US 6,245,331

D5: WO 1999/00671

D6: US 5,670,312

D7: Kronberg et al. (1992)

D8: Romain et al. (1993)

D9: Ranadive et al. (1986)

Each of these documents will be discussed below.

NOVELTY and INVENTIVE STEP: Claims 1-198

D1: This document discloses a method for the identification and isolation of *Pasteurella haemolytica* antigens. This may be achieved through an immunoaffinity column which utilises immune sera from pasteurellosis-infected cattle to selectively purify antigenic peptides. This document anticipates claims 43-56, 65-68 and 128-133, 135, 136, 140-152, 161-165, 167-172 and 193-196. Claims 57-64, 69, 70, 134, 137-139, 153-160, 166, 173 and 174 are not inventive as the features of these claims represent either subject matter which is well known to a person skilled in this art or alternatives which would have been obvious to the skilled person.

D2: This document relates to immune complex isolation and methods for diagnosing diseases. A reagent RhC is used to precipitate the immune complexes from serum. The immune complex with RhC can then be immobilized on a protein A column. The complexes are then eluted using glycine. The antigens are separated by SDS-PAGE electrophoresis and an antigen 'profile' may be generated. This document deprives claims 1-21, 26, 27, 34-38 and 193-195 of novelty. Claims 22-25, 28-33 and 39-42 are not regarded as inventive, as these features are well known to a person skilled in this art, or represent merely alternatives which would be obvious to the skilled person.

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

1. Claim 125 appears to be incorrectly appended to claim 104. It is supposed that this should be appended to claim 124.

2. Claim 43 refers to step (ii) twice.

Supplemental Box Relating to Sequence Listing

Continuation of Box No. I, item 2:

1. With regard to any nucleotide and/or amino acid sequence disclosed in the international application and necessary to the claimed invention, this report was established on the basis of:
   a. type of material
      [X] a sequence listing
      [ ] table(s) related to the sequence listing
   b. format of material
      [X] in written format
      [X] in computer readable form
   c. time of filing/furnishing
      [X] contained in the international application as filed
      [X] filed together with the international application in computer readable form
      [ ] furnished subsequently to this Authority for the purposes of search and/or examination
      [ ] received by this Authority as an amendment* on
2. [ ] In addition, in the case that more than one version or copy of a sequence listing and/or table(s) relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.
3. Additional comments:

* *If item 4 in Box No. I applies, the listing and/or table(s) related thereto, which form part of the basis of the report, may be marked "superseded."*

Supplemental Box

In case the space in any of the preceding boxes is not sufficient.

Continuation of: **BOX V**

D3: This document discloses a method of identifying a Mycobacterium species responsible for a mycobacterial infection in a human or animal. The method involves exposing the antibodies from the serum of an infected individual to an antigenic preparation and thereby identifying antigens. This document deprives claims 43-54, 65-70 and 193-196 of novelty. Claims 55-64 and 128-174 are not regarded as inventive as the features of these claims are regarded as well known to a person skilled in the art or represent merely alternatives which would be obvious to the skilled person.

D4: This document discloses a method for the early detection of mycobacterial disease. In particular, the disclosure in column 21 from line 8 describing a method for identifying and isolating early Mt antigens. This involves immunocapture using an adsorbed patient serum. There is a disclosure in column 22 from line 31 describing the detection of immune complexes containing early Mt antigens. This suggests that it is known to isolate complexes which can then be dissociated. This document is considered to deprive claims 1-14, 17-21, 23-25, 36, 43-56, 65-70 and 193-196 of novelty. Claims 15, 16, 22, 26-35, 37-42, 57-64 and 128-174 are not regarded as inventive as the features of these claims are well known in the art or would be obvious to a person skilled in the art.

D5:This document discloses a method for the identification of cellular protein antigens of patients with cancer which involves the use of patient derived sera. The antigen-containing protein mixture is separated by 2D electrophoresis. The proteins which are bound are identified as proteins to which a subject with cancer produces autoantibodies (ie. they are immunogenic). The separated proteins may be used for immunization or for immunoassays. This document is considered to deprive claims 43-54, 65, 71-86 and 193-197 of novelty. Claims 55-64, 66-70, 87-174 and 198 are not regarded as inventive as the features of these claims are either well known in the art or would be obvious to the person skilled in the art.

D6: This document discloses a method for isolating peptides and/or other molecules which specifically bind to antibodies in sera. The antibodies are immobilized on a solid support and a library of peptides is brought into contact with the antibodies. Any non-disease specific antibodies from a second patient sample will not bind with the peptides isolated by this method, therefore only disease specific peptides are identified. This document deprives claims 43-58, 65, 193-195 of novelty. Claims 59-64, 66-174 and 196-198 are not regarded as inventive as these claims contain features which are either well known in the art or would be obvious to the person skilled in the art.

D7: This document discloses the separation and identification of antigenic components of immune complexes in CF sputum using SDS-PAGE and immunoblotting. ICs were precipitated with PEG then analysed by SDS-PAGE before transfer to nitrocellulose. These transferred were probed with, among others, pooled sera from CF patients chronically infected with *P.aeruginosa*. The authors demonstrate the existence of ICs consisting of LPS and anti-LPS antibodies. This document is considered to deprive claims 1-10, 17-22, 24-27, 34-36, 193-196 and 198 of novelty. Claims 11-16, 23, 28-33 and 37-42 are not regarded as inventive as these claims contain features which are either well known in the art or would be obvious to the person skilled in the art.

D8: This document relates to the biochemical characterization of a complex of antigens which interact with antibodies present in serum of guinea pigs immunized with BCG. This document is considered to deprive claims 43-54, 65-70 , 128-150, 193-196 of novelty. Claims 55-64 and 151-160 are not regarded as inventive as the features are either well known or would be obvious to the person skilled in the art.

D9: This document describes a study of antigens from Mycobacterium tuberculosis that cause a humoral response using immunoaffinity, SDS-PAGE and autoradiography. This document is considered to deprive claims 43-56, 65-70 and 193-196 of novelty and claims 57-64 and 128-174 cannot be regarded as inventive as the features of these claims are regarded as well known or would be obvious to the person skilled in the art.

upplemental Box

n case the space in any of the preceding boxes is not sufficient.

Continuation of: **BOX V**

n general, it is to be noted that, as drafted, claims 43, 71, 95 and 128 appear to define nothing more than a standard mmunoassay or immunoaffinity process.

Part (i) of claim 43, for example, defines a step of "obtaining a protein complex comprising an immunoglobulin or nixtures thereof or an immunoglobulin-containing fraction from a subject suffering from the disease or disorder or aving suffered previously from the disease or disorder or a cell, tissue or organ thereof". It is well known that an mmunoglobulin-containing fraction can be isolated from a biological sample through precipitation (ammonium ulphate or PEG) or adsorption to a suitable material such as Protein A or Protein G.

Part (ii) of claim 43 defines a step of "contacting immunoglobulin in the protein complex or immunoglobulin-containing fraction with a sample comprising the agent that causes the disease or disorder thereof". It is well known to use an immunoglobulin-containing fraction to adsorb to a column or microtitre plate such that it can be utilised for the mmunocapture of binding molecules. A sample containing an agent (or antigen) of interest is then contacted with the adsorbed immunoglobulin-containing fraction. The sample is broadly defined and can encompass any sample such as antisera or a mixture of antigenic molecules.

Part (iii) of claim 43 defines a step of "identifying a protein or fragment thereof bound to said immunoglobulin by virtue of an antigen-antibody interaction". This step is broadly defined and encompasses the identification of an antigen which binds to an immunoglobulin through any well known immunological assay means such as immunofluorescence, ELISA etc.. It is also well known elute the bound molecules, either together with the immunoglobulin or as separate fractions, from an immunaffinity column and subsequently assay for the presence of a specific molecule. It is also well known to use SDS-PAGE or chromatography for the separation of proteins which can then be identified and isolated.

The purpose of many immunological testing methods is to identify antigenic molecules which are then tested to determine whether they can stimulate an immune response. This is performed, for example, by immunizing an animal and testing to determine whether antibodies are raised against the particular immunogen.